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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/670,490	09/25/2003	Eytan R. Barnea	120785.0310	8761

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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 06/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/670,490	BARNEA ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-24 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-24 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11/10/04 1/2/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-24 are pending and examined on the merits.

Priority

Acknowledgement is made of applicants claim to an earlier effective filing date through 09/720,693, filed February 21, 2001, PCT/US99/14834, filed June 30, 1999 which claimed benefit of provisional applications 60/091,579, filed July 2, 1998 and 60/119,264, filed February 9, 1999. Further, it is noted that the earliest of the provisional applications, 60/091,579 provides no description of the high molecular weight embryonic fractions of the activities thereof; the second provisional application 60/119,264 while providing a description of the high molecular weigh embryonic fraction of the instant invention, fails to provide support for the anti-tumor activity thereof as it is concerned with only the anti-viral activity. Thus, claims 1-14 drawn to methods for inhibiting cancer comprising the administration of the high molecular weigh extracts, would be given the benefit of an earlier effective filing date corresponding to PCT/US99/14834, filed June 30, 1999. Claims 15-21, drawn to methods for inhibiting viral infection comprising administration of the high molecular weight extracts, would be given the effective filing date of 60/119,264, filed February 9, 1999. Claims 22-24, drawn to the peptides of SEQ ID NO:1-12 and methods of using said peptides to inhibit the proliferation of cancer cells, would be given priority to 60/091,579, filed July 2, 1998.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 15-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites "not substantially retained by DEAE resin". The metes and bounds of "not substantially retained" cannot be construed. It is unclear if applicant intends that the protein

would pass through the DEAE resin in the void volume, or if applicant intends that some degree of salt would be necessary to elute the protein. Further, one of skill in the art would not be able to determine if elution with a given salt concentration would be commensurate with "not substantially retained", such as 0:1M NaCl or 0.25 M NaCl.

Claim 9 recites administering an "effective amount" of the composition of claim 1 to a subject in order to inhibit "the effects" of a viral infection. In this case, the metes and bounds of "effective amount" are unclear because said effective amount is targeted to inhibiting the "effects" of a viral infection rather than inhibiting the proliferation of the virus. It is unclear what applicant intends to encompass within "the effects" of a virus which can include serious effects such as T-cell deficiencies and less serious effects, such as headache and malaise in a rhino virus infection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A) as drawn to the written description of the therapeutic compositions and methods reliant thereon of claims 1-21.

Claims 1-8 are drawn to therapeutic compositions comprising one or more antiproliferative proteins as comprised in a high molecular weight fraction of an embryonal extract, wherein said proteins has a molecular weight greater than 10 kDa and inhibits the proliferation of a cancer cell. Claims 9-21 are methods reliant on the description of the therapeutic composition. When given the broadest reasonable interpretation, the therapeutic composition is a genus of proteins include any protein which has a molecular weight greater than

10 kDa and can be found in an embryonal extract, wherein said protein can inhibit the proliferation of a cancer cell. The genus is highly variant because it does not limit the organs or species used to obtain the embryonal extract. The art recognizes that embryonal extracts from different organ systems provides fractions having differing activities (note Barnea et al, 1996 below specifically uses spinal cord and brain). The instant specification describes an embryonal extract obtained from porcine liver, and the antiproliferative fractions obtained therefrom. The description of antiproliferative fractions obtained from embryonic pig liver does not adequately describe the claimed genus of therapeutic compositions claimed because the genus tolerates members, such as proteins which are not present in embryonic liver.

One of skill in the art would reasonably conclude that applicant was not in possession of the genus of therapeutic compositions claimed.

(B)As drawn to the written description of the peptides of claim 22 and methods reliant thereon.

Claim 22 is drawn to the peptides of claim 22. When given the broadest reasonable interpretation the claim can include antiproliferative peptides comprising SEQ ID NO:1-12 rather than consisting of said peptides. Thus the genus of antiproliferative peptides is variant because said genus tolerates members which only minimally comprise SEQ ID NO:1-12, thus requiring only 7 amino acids of the described peptides and some degree of antiproliferative property to be included within the genus. The description of the peptides consisting of SEQ ID NO:1-12 fails to describe the claimed genus because the genus tolerates members which differ widely in structure from the instant SEQ ID NO:1-12 because 7 contiguous amino acids could be dominated by a much larger peptide having completely different mechanism of exerting an antiproliferative action that that of the instant SEQ IDNO:1-12. Amendment of claim 22 to read unambiguously on peptides consisting of SEQ ID NO:1-12 would overcome this rejection.

Claims 15-21 are drawn to a method of inhibiting the effects of a viral infection in a subject comprising administering an effective amount of the therapeutic composition of claim 1. The specification teaches that the high molecular weigh composition of claim 1 was used to measure the EC50 versus the CC50 in virally infected cells in culture to obtain a selectivity index (page 14, lines 22-26). This method of inhibiting toxicity to virally infected cells is not commensurate with inhibiting the "effects" of a viral infection in a subject, because said effects

can result from secondary effects resulting from the response of the individuals immune system against the virus. Thus the disclosure of the toxicity data reported on pages 15-21 does not adequately describe the claimed method of inhibiting the "effects" of a viral infection. One of skill in the art would reasonable conclude that applicant was not in possession of a broad method to inhibit the "effects" of a viral infection.

Claims 22-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting the proliferation of cancer cells comprising the administration of the peptides consisting of SEQ ID NO:2, 3 or 8, does not reasonably provide enablement for a method of using SEQ ID NO:1, 4-7 or 9-12. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification states that the mixture of peptides corresponding to SEQ ID NO:1-12 possessed no inhibitory activity against MCF-7 cells, but that SEQ ID NO:2, 3and 8 possessed significant inhibitory activity, and explains that the remainder of the peptides are able to compete with the active peptides for receptor sites on MCF-7, but do not possess inhibitory activity (page 26, line 22 to page 27, line 13). Thus is appears that SEQ ID NO:1, 4-7 and 9-12 are not antiproliferative peptides having activity against cancer cells. One of skill in the art would be subject to undue experimentation in order to carry out the method of claim 22 with peptides other than SEQ ID NO:2, 3 or 8. One of skill in the art would also be subject to undue experimentation in order to use the peptides SEQ ID NO:1, 4-7 and 9-12 of claim 22 because said peptides would not be expected to have anti-proliferative activity and the instant specification has not provided any alternative teachings regarding how to use the claimed peptides.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in
(1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent,; or
(2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 22-24 are rejected under 35 U.S.C. 102(e) as being anticipated by Barnea (U.S. 5,648,340).

Claim 22 is drawn to an antiproliferative peptide selected from the group consisting of SEQ ID NO:1-12. Claim 23 is drawn to a method of inhibiting the proliferation of cancer cells in a subject comprising administering to said subject an effective amount of a peptide according to claim 22. Claim 24 is drawn to a method of inhibiting the proliferation of cancer cells in a subject comprising administering to the subject an effective amount of a peptide selected from SEQ ID NO:2, 3 and 8.

Barnea discloses an antiproliferative embryonic fraction having a molecular weight of less than 8 kDa (column 18, Table III). Barnea et al discloses that the embryonic tissue is solublized by sonication, subjected to centrifugation to remove cellular debris (column 7, lines 43-51). Barnea discloses that the resulting supernatant is then fractionated by molecular weight, using as an example, a gel filtration system (column 7, lines 54-59). Barnea discloses a separation step comprising a DEAE column (column 20, lines 56-61). The anti-proliferative fraction of Barnea would inherently comprise a peptide of SEQ ID NO:1-12 because the origin of the material from when SEQ ID NO:1-12 were obtained is the same as the origin of the material used for the antiproliferative fraction of Barnea. Barnea discloses a method for treating cancer in a patient including breast, ovary, kidney, lung brain intestine, bone marrow, lympho-

reticulo, stomach esophagus, pancreas, spinal cord mucosa, germ cell, bone, muscle, melanoma and choriocarcinoma (column 11, lines 29-35).

Claims 1, 2 and 9-11, 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Barnea (U.S. 5,648,340).

Barnea discloses a high molecular weigh fraction of porcine or human embryonic spinal cord (column 22, Table IV and column 22, line 60 to column 23, line 4 and column 23, Table V and lines 57-64) wherein the molecular weigh was determined to be between 10 and 15 kDa for JDK-AP1 (column 26, lines 7-9). Barnea et al discloses that the embryonic tissue is solublized by sonication, subjected to centrifugation to remove cellular debris (column 7, lines 43-51). Barnea discloses that the resulting supernatant is then fractionated by molecular weight, using as an example, a gel filtration system (column 7, lines 54-59). Barnea discloses a separation step comprising a DEAE column (column 20, lines 56-61). Barnea discloses a method for treating cancer in a patient including breast, ovary, kidney, lung brain intestine, bone marrow, lympho-reticulo, stomach esophagus, pancreas, spinal cord mucosa, germ cell, bone, muscle, melanoma and choriocarcinoma (column 11, lines 29-35)

Claims 1 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Barnea et al American Journal of Reproductive Immunology, 1996, Vol. 35, pp. 318-324).

Barnea et al disclose a human embryonal extract made by sonicating spinal cord and brain tissue, centrifugation and supernatant filtration (page 319, 2nd column, lines 1-7) followed by size exclusion chromatography (page 319, 2nd column, lines 9-16), to obtain fraction A of 4.5 kDa and fraction B of 10.7 kDa both of which caused an inhibitory effect on the proliferation of MCF-7 cells (page 320, 1st column, lines 16-23). Barnea discloses that a fraction of less than 8 kDa had a slight but significant inhibitory effect on the proliferation of MCF-7 cell lines. The antiproliferative peptides of claim 22 would inherently be present in the fraction of less than 8 kDa because said fraction is made from the same stating tissue and separated by the same method as the instant peptides.

Claims 1-3 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Cavanaugh et al (U.S. 5,393,534) in view of Brill et al, (Proceedings of the Society for Experimental Biology and Medicine, 1993, Vol. 204, pp. 261-269).

Claim 1 is drawn to a therapeutic composition comprising one or more antiproliferative protein as comprised in a high molecular weight fraction of an embryonal extract prepared by the steps of: a) solublizing a mammalian embryonal tissue; b) centrifuging the solublized embryonal tissue to form a supernatant; c) applying the supernatant to a gel filtration column; d) eluting the gel filtration column; e) collecting the eluate as serial fractions; and f) identifying one or more fraction that contains a protein having a molecular weight greater than 10 kDa and which inhibits the proliferation of a cancer cell; whereby the identified fraction or fractions contains one or more antiproliferative protein. Claim 2 embodies the therapeutic composition of claim 1 where the protein is comprised in an extract purified by steps a) through f) and further purified by DEAE chromatography, where the protein is not substantially retained by DEAE resin. Claim 3 embodies the therapeutic composition of claim 1, where the protein has a molecular weight of between 30 and 80 kDa. Claim 6 embodies the therapeutic composition of claim 1 where the protein has a molecular weight of approximately 40-42 kDa.

Cavanaugh et al disclose a protein prepared from an extract of liver homogenate, said extract having a growth inhibitory effect on large cell lymphoma, and melanoma, mammary carcinoma and metastatic lung cell culture lines (column 15, lines 33-48). Cavanaugh et al disclose that the fraction having inhibitory activity had a molecular weight of 38 kDa to 40 kDa (abstract).

Claims 1-3 and 6 are product by process claims. The MPEP (2113) states

PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable

even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985)

In the instant case, the composition of Cavanaugh et al appears to have the same molecular weight and anti-cancer activity as the instant claimed compositions even though Cavanaugh et al isolated the inhibitor fractions from liver homogenates rather than embryonal homogenates. The prior art (abstract of Brill et al, Proceedings of the Society for Experimental Biology and Medicine, 1993, Vol. 204, pp. 261-269) recognizes the presence of hepatic progenitor cell populations within the adult liver. Said progenitor cells would have an embryonic phenotype and express proteins consistent with an embryo. Thus, it appears that the liver extracts of Cavanaugh et al possess the same inhibitory proteins as that obtained from an embryo extract.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9-11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cavanaugh et al (U.S. 5,393,534).

Claim 9 is drawn to a method of inhibiting the proliferation of cancer cells in a subject comprising administering, to the subject, an effective amount of the therapeutic composition of claim 1. Claim 10 embodies the method of claim 9, where the cancer cells are breast cancer cells. Claim 11 embodies the method of claim 9, where the cancer cells are lung cancer cells. Claim 13 embodies the method of claim 9, where the cancer cells are melanoma cells.

Cavanaugh et al teach a protein prepared from an extract of liver homogenate, said extract having a growth inhibitory effect on large cell lymphoma, and melanoma, mammary carcinoma and metastatic lung cell culture lines (column 15, lines 33-48) which fulfills the specific embodiment of claims 1-3 and 6, for the reasons set forth above.. Cavanaugh et al suggest that because the inhibitory liver extract is able to differentially inhibit the growth of metastatic and non-metastatic tumor cells, said inhibitor will have use in a clinical setting in human subjects in need thereof (column 16, lines 1-6).

It would have been prima facie obvious at the time the claimed invention was made to treat patients having large cell lymphoma, melanoma, breast and lung cancer with the inhibitory fractions taught by Cavanaugh et al. One of skill in the art would have been motivated to do so by the suggestion of Cavanaugh that said inhibitory extracts would be useful in a clinical setting and in particular would be useful as anti-metastatic agents.

Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Ajinomotot (Biotech on STN, The Thomson Corp), JP 60178820, 12 September 1985) in view of Barnea et al (American Journal of Reproductive Immunology, 1996, Vol. 35, pp. 318-324, reference of the IDS filed Nov. 10, 2004)

The abstract of Ajinomoto teaches an extract of cattle embryonic cartilage wherein a crude extract is purified by membrane fractionation and adsorption on DEAE-agarose. The abstract teaches that the antitumor substance in the extract has a molecular weight of 100 kDa to 300 kDa and is obtained by elution with 0.25M-0.6M NaCl. The abstract does not teach centrifugation of solublized embryonic tissue to form a supernatant.

Barnea et al teach that an embryonic extract was subjected to centrifugation before the filtration step.

It would have been prima facie obvious at the time the claimed invention was made to subject the crude extract of the abstract of Ajinomotot to a centrifugation step before the membrane fractionation step. One of skill in the art would have been motivated to do so by the teachings of Barnea et al on the centrifugation of the solublized embryonic material before the filtration step. One would have been motivated to do so in order to remove particulates that could interfere with the membrane separation by physically blocking the membrane.

All claims are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
5/30/2006

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PRIMARY EXAMINER